INVESTOR IN PEOPLE

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South Wales
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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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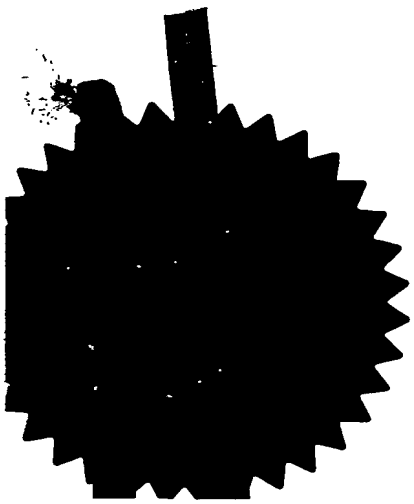


Signed

Dated 24 January 2005

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
12 DEC 2003
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

REP07618GB

2. Patent application number
(The Patent Office will fill this part in)

0328871.9

12 DEC 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arakis Ltd.
Chesterford Research Park
Little Chesterford
Saffron Walden
Essex CB10 1XL

Patents ADP number *(if you know it)*

8306128001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Resolution Process

5. Name of your agent *(if you have one)*

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)*

745002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	5
Claim(s)	1
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	NO
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature

Date 12 December 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward
020 7377 1377

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

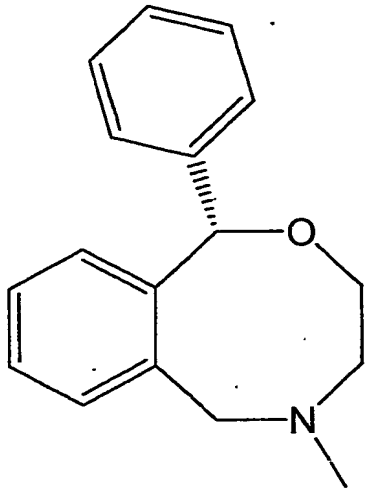
RESOLUTION PROCESS

Field of the Invention

The present invention relates to a process for the manufacture of the single enantiomers of nefopam and analogues.

Background to the Invention

Nefopam is a chiral drug substance developed for the treatment of moderate to severe pain. Although nefopam is marketed as a racemic mixture, both enantiomers of the drug have been shown to exhibit different biological activities. *In vitro* and *in vivo* studies have shown that (+)-nefopam has more potent analgesic and dopamine, norepinephrine and serotonin-uptake inhibitory properties than (-)-nefopam (Fasmer et al., 1987; Rosland and Hole, 1990; Mather et al., 2001). Nefopam has been disclosed (PCT/GB03/02586) to have utility in the treatment of emesis and related conditions with (+)-nefopam being the preferred enantiomer.



(1)

An efficient and reliable method for the preparation of the individual enantiomers of nefopam and nefopam analogues is desirable. As racemic nefopam is readily available, a classical resolution process, involving separation of diastereoisomeric salts by selective crystallisation may be suitable.

Summary of the Invention

This invention is based on the surprising discovery that racemic nefopam and analogues can be resolved efficiently, using the substantially single enantiomers of *O,O*-dibenzoyltartaric acid or a related *O,O*-aroyltartaric acid as a resolving agent.

Description of the Invention

The compounds resolved according to the invention are selected from nefopam and nefopam analogues. The process of this invention may be carried out under conditions that are generally known to those skilled in the art of classical optical resolution methods.

In a typical experiment, nefopam was dissolved in ethanol then treated with a solution of *O,O*-dibenzoyl-L-tartaric acid monohydrate (1.0 mol equivalent). The resulting solution was allowed to stand until precipitation occurred. Collection of the solid and recrystallisation produced the (+)-bis-nefopam *O,O*-dibenzoyl-L-tartaric salt in 22% yield and 99% enantiomeric excess.

Since both enantiomers of *O,O*-dibenzoyltartaric are readily available in quantity, either can be used to effect the resolution depending on which enantiomer of nefopam is required. Thus, (-)-bis-nefopam *O,O*-dibenzoyl-D-tartaric salt could be prepared in a similar yield and optical purity utilizing *O,O*-di-*p*-toluoyl-D-tartaric acid as the resolving agent.

This resolving agent may also be used to increase the optical purity of enantiomerically-enriched nefopam. Thus, when both enantiomers of nefopam are required, the processes described above can be compressed, one enantiomer being recovered by the resolution and the opposite enantiomer being extracted from the mother liquors of the resolution. In practice, when (+)-bis-nefopam *O,O*-dibenzoyl-L-tartaric salt is recovered as described above, the mother liquors remaining are processed to isolate nefopam free base enriched in the (-)-isomer, which is then purified by treatment with *O,O*-dibenzoyl-D-tartaric and crystallization of the resultant salt.

The yield of the resolution procedure can be improved by a reverse resolution process. Thus, when racemic nefopam is treated with *O,O*-di-*p*-

toluoyl-D-tartaric acid, (-)-bis-nefopam *O,O*-dibenzoyl-D-tartaric salt is isolated. The mother liquors now enriched with (+) nefopam can be resolved in the normal way using *O,O*-dibenzoyl-L-tartaric acid to give (+)-bis-nefopam *O,O*-dibenzoyl-L-tartaric salt in good yield. The same reverse resolution process can be applied to the isolation of (-)-bis-nefopam *O,O*-dibenzoyl-L-tartaric salt in good yield

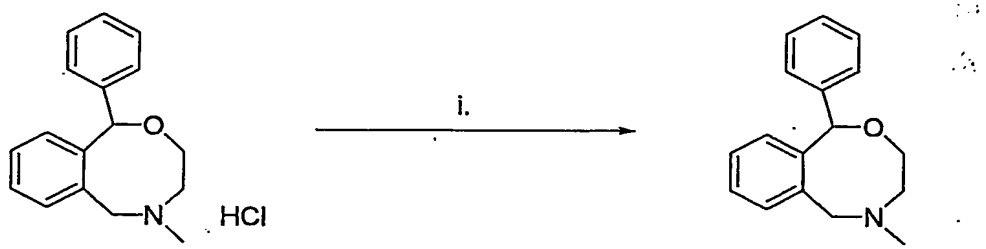
Other beneficial aspects of the process of the present invention can be summarized as follows:

1. The resolving agent can be easily recovered in a state of high purity, such that it can be re-used in one or more subsequent resolution processes.
2. If desired, less than 1.0 molar equivalent of resolving agent may be used in the process.

A substantially single enantiomer that is used in or produced by the process of the invention may be in at least 80% ee, preferably at least 90% ee, more preferably at least 95% ee, and most preferably at least 98% ee.

The present invention is illustrated by the following Examples.

Example 1 **Nefopam freebase**



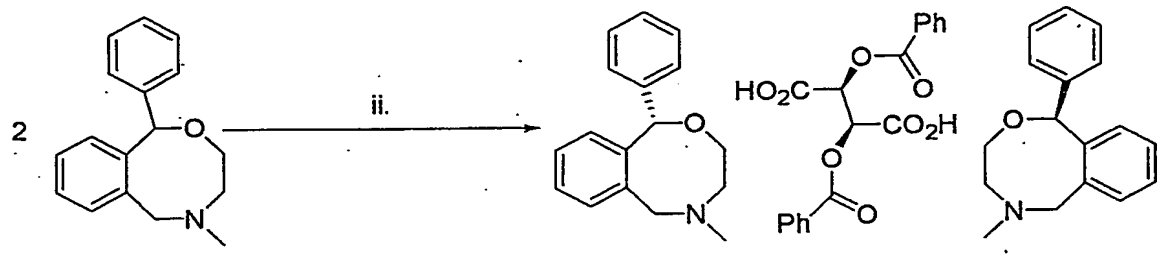
$C_{17}H_{20}ClNO$
Mol. Wt.: 289.80

$C_{17}H_{19}NO$
Mol. Wt.: 253.34

Racemic nefopam hydrochloride (5.0Kg, 17.2mol) was suspended in water (12.5L) and 2M sodium hydroxide solution (18.5Kg) and solid sodium hydroxide (50g) added. Ethyl acetate (11.16Kg) was added and the mixture stirred for 10 minutes until complete dissolution was achieved. Stirring was stopped and two layers separated out. The ethyl acetate layer was removed and stored. The aqueous layer was further extracted with ethyl acetate (11.16Kg) and the combined ethyl acetate extracts dried with magnesium sulphate (500g), filtered and evaporated to furnish the product as a colourless semi solid. The

above process was repeated and furnished the product in quantitative yield (9.31Kg, 106%, contained residual ethyl acetate).

Example 2 **(+)-Bis-nefopam-*O,O*-dibenzoyl-l-tartaric acid salt**



$C_{17}H_{19}NO$
Mol. Wt.: 253.34

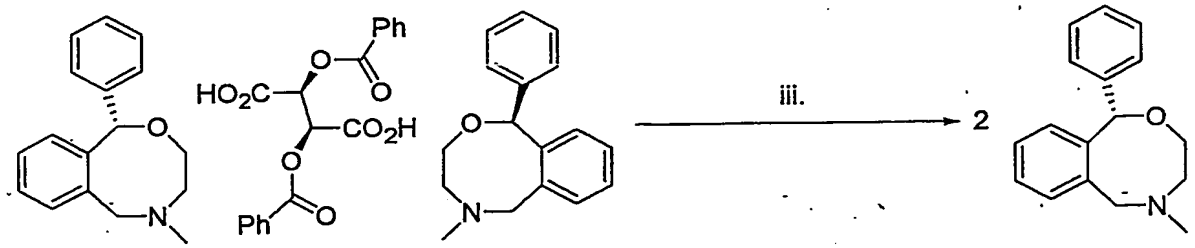
$C_{52}H_{52}N_2O_{10}$
Mol. Wt.: 864.98

The isolated product of Example 1 (7.86Kg, 31.0mol) was dissolved in ethanol (14.7Kg) and stirred at room temperature. A solution of *O,O*-dibenzoyl-l-tartaric acid (2.75Kg, 0.25 mol equiv.) in ethanol (16.0Kg) was added over a period of 20 minutes. The resulting solution was allowed to stir at room temperature overnight during which time crystallisation occurred. The crystals were collected by filtration, washed with ethanol (2 x 2L) and dried to constant weight at 45°C under reduced pressure. The product was obtained as a colourless solid, 4.27Kg, 32%. Chiral HPLC indicated 83% e.e. for (+)-nefopam.

The solid was recrystallised in two batches from ethanol (2 x 12.16Kg) and the solid washed with ethyl acetate (2 x 2L). The combined solid was dried to constant weight at 45°C under reduced pressure to furnish the product as a colourless solid, 2.90Kg, 68%. Chiral HPLC analysis indicated 99% e.e.

Resolution concentration uses 5 volumes of ethanol with an overall 22% yield.

Example 3 **(+)-Nefopam**

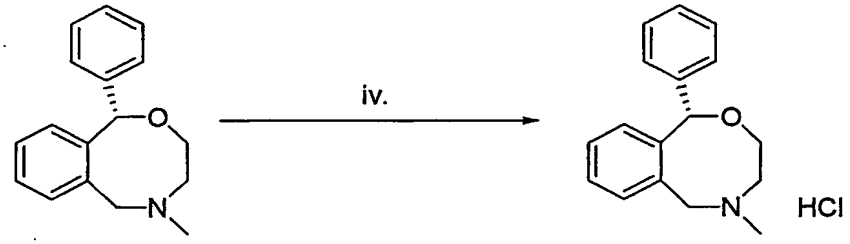


$C_{52}H_{52}N_2O_{10}$
Mol. Wt.: 864.98

$C_{17}H_{19}NO$
Mol. Wt.: 253.34

Sodium hydroxide (335g, 8.38mol, 2.5equiv.) was dissolved in water (11.9Kg) and the solution added to the isolated product of Example 2 (2.89Kg, 3.34mol). The mixture was stirred for 10 minutes and extracted with ethyl acetate (3 x 4.38Kg). The ethyl acetate extracts were dried with magnesium sulphate (500g), filtered and evaporated under reduced pressure to constant weight. The product was isolated as colourless oil, 1.53Kg, 90%.

Example 4 **(+)-Nefopam, hydrochloride salt**



$C_{17}H_{19}NO$
Mol. Wt.: 253.34

$C_{17}H_{20}ClNO$
Mol. Wt.: 289.80

The isolated product of Example 3 (1.53Kg) was dissolved in *iso*-propanol (4.81L) and the resulting solution heated to 50°C. Concentrated hydrochloric acid (498mL) was added over 15 minutes followed by stirring at 50°C for 10 minutes. The solution was allowed to cool to 30°C followed by cooling in an ice/salt bath to 0°C (precipitation begins at @ 35°C). The mixture was stirred for a further 1 hour at 0°C. The precipitate was filtered and washed with cold *iso*-propanol (2 x 1.05L) and the solid dried in the vacuum oven at 35°C. The product was obtained as a colourless solid, 1.05Kg, 96.7% e.e.

On standing overnight the further product precipitated. The precipitate was filtered and washed with isopropanol (2 x 0.5L) and dried in the vacuum oven at 35°C. The product was obtained as a colourless solid, 0.51Kg, 99% e.e. Total yield 1.56Kg, 89%

CLAIMS

1. A process for increasing the optical purity of a mixture of enantiomers of nefopam or a nefopam analogue, using a substantially single enantiomer of a *O,O*-diaroyltartaric acid as a resolving agent.

2. A process according to claim 1, for preparing a substantially single enantiomer of nefopam or a nefopam analogue, which proceeds by means of resolution of racemic nefopam or nefopam analogue, using a substantially single enantiomer of a *O,O*-dibenzoyltartaric acid as a resolving agent.

3. A process for preparing a substantially single enantiomer of nefopam or a nefopam analogue, which proceeds by means of a reverse resolution of racemic nefopam or nefopam analogue, using sequentially a single enantiomer of a *O,O*-dibenzoyltartaric acid as a resolving agent and then the other enantiomer.

4. A process according to any of claims 1 to 3, for preparing substantially single enantiomer (+)-nefopam, which uses *O,O*-dibenzoyl-L-tartaric acid as the resolving agent.

5. A process according to any of claims 1 to 3, for preparing substantially single enantiomer (-)-nefopam or a pharmaceutically acceptable salt thereof, which uses *O,O*-dibenzoyl-D-tartaric acid as the resolving agent.

6. A process according to any preceding claim, which is conducted in a solvent selected from alcohols, esters, ketones and halogenated solvents.

7. A process according to any preceding claim, which comprises the further step of conversion of the salt obtained by the resolution to the free base form of nefopam or a pharmaceutically acceptable salt thereof.

Document made available under the Patent Cooperation Treaty (PCT)

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